

## Menstrual Cycle in Schizophrenic Patients: Review with a Case

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### ABSTRACT

There are not enough studies about the relationship between menstrual psychosis and schizophrenia exacerbation during the menstrual cycle. In patients diagnosed with schizophrenia, it is important to examine the psychotic symptoms and depression and anxiety symptoms during the menstrual cycle and to adjust the treatment according to these symptoms. If depression and anxiety symptoms are present, selective serotonin reuptake inhibitors can be used. In patients with exacerbated psychotic symptoms, it may be effective to increase the dose of an

antipsychotic drug, which has no effect on prolactin release, 3–5 days prior to menstruation. In addition, hormonal therapy or menstrual cycle suppression is an alternative option. In this article, a case of a schizophrenic patient whose psychotic symptoms exacerbated with the menstrual cycle is presented.

**Keywords:** Schizophrenia, estrogen, menstrual psychosis

### INTRODUCTION

It has been reported in many studies that estrogen has a significant impact on the psychological state of women. It is known that schizophrenia initiates in the older age and shows a better clinical course in women than in men (1,2). It is thought that estrogen is protective against schizophrenia with its antidopaminergic effect (3,4). Furthermore, seeing a second peak in the prevalence of schizophrenia during the postmenopausal period in women could be evidence of the protective effect of estrogen against schizophrenia (3). It was also structurally shown that a decrease in the cortical gray substance volume and ventricular expansion was higher in female than in male patients with schizophrenia (5). Moreover, it is known that lower doses of antipsychotic treatment are sufficient in female patients than in male patients with schizophrenia and that antipsychotic doses may need to be increased during the postmenopausal period in women (6,7). It was shown that there is a negative relation between blood estradiol levels and negative findings of schizophrenia and that schizophrenia finding intensity decreases as estradiol levels increase (8,9). It is known that estrogens have protective effects on neurons and that 17 $\beta$ -estradiol, in particular, is effective in psychological and behavioral sexual differentiation during the intrauterine period for both genders (10). Estrogen shows its impacts on the central nervous system by changes in cognition, mood, and behavior. Estrogen receptors are widely spread in the brain, including the cerebral cortex, hypophysis, and limbic systems (11).

It was shown that in female schizophrenic patients, the intensity of the disease is changeable during the menstrual cycle and that deterioration is likely to be during low estrogen phases. The intensity of the disease usually reduces during pregnancy. However, recurrences are usually observed during the postpartum period (12,13).

This case was introduced to highlight the effect of the menstrual cycle, and thus estrogen, on female schizophrenic patients.

### CASE

Our patient is a 50-year-old primary school graduate, single, and unemployed female who lives with her family. She applied to our psychiatry outpatient clinic because of complaints of insomnia, hallucination, and irritability.

Her complaints began at the age of 14 years with soliloquy, temper, insomnia, hearing voices, and skepticism. During that period, she used medications, the names of which she could not remember, prescribed by a psychiatrist. She took her medications only during the attacks until she was approximately 30 years. For the last two decades, she has been regularly followed-up because of a diagnosis of schizophrenia, and during that period, she used various antipsychotic medications such as haloperidol, trifluoperazine, and risperidone. Finally, we found out that she had been taking amisulpride at 800 mg/day for the last eight months.



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**Received:** 14.02.2014 **Accepted:** 03.07.2014

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Her appearance and self-care were poor. Her psychomotor activity was high. She was talking clearly and understandably but slowly, and her associations were loose and goal-oriented. Inappropriate effect was observed. Her cognitive abilities were normally assessed. Visual and auditory hallucinations and persecutory and reference delusions were defined. Her reality testing was destroyed. Amenorrhea was observed for the past year.

### Laboratory and Imaging Studies

To exclude her general medical condition, brain magnetic resonance imaging (MRI), electroencephalogram (EEG), hematologic and thyroid function parameters, and serum vitamin B12, folic acid, and serum prolactin levels were tested. The MRI and EEG results were normal. Her vitamin B12 level was 170 pg/mL (normal: 220–940 pg/mL), and her prolactin level was 130.6 µg/L (normal: 6–29 µg/L).

### Clinical Observation

Parenteral vitamin B12 treatment was introduced until the vitamin B12 level reached the normal values. High prolactin levels and amenorrhea observed in the patient were thought to result from the amisulpride treatment. Thus, the amisulpride dose was gradually reduced and quetiapine treatment was introduced, and the quetiapine dose was gradually increased to 600 mg/day after one week. With this treatment, psychotic findings of the patient regressed. Her prolactin levels began to decrease and regressed to the normal levels at the end of the third month. After the fourth month, her menstrual cycle became regulated.

During the six-month monitoring period, attacks were observed characterized by auditory and visual hallucinations, irritability, insomnia, and psychomotor agitation starting two days before menstruation. During her clinical observation, the quetiapine dose was increased to 800 mg/day for one month. During the period of the attacks, chlorpromazine 100 mg/day was initiated. During some attack periods, zuclopenthixol acuphase injections were made. Each time, the findings of the patient regressed within three days.

### DISCUSSION

The relation between schizophrenia and the menstrual cycle has always been found attractive by researchers. It is accepted that female reproductive hormones regulate the functions of neurotransmitters such as serotonin, dopamine, norepinephrine, and gamma-aminobutyric acid and that hormone fluctuations may lead to mental complaints (14). It was reported that there could be fluctuations in the psychotic findings of schizophrenic patients during the menstrual cycle and that in the phases where estrogen levels are low, the intensity of the disease may be higher (15,16,17). The fact that schizophrenia is observed earlier in male than in female patients and displays a better course in female patients made estrogen a focus of interest. On the other hand, it is still a question of debate whether the clinical picture deteriorates because of hormonal changes during the perimenstrual period or because of the addition of premenstrual syndrome on psychotic findings accompanied by anxiety, depression, and somatic complaints (18). Increase in estrogen sensitivity in dopaminergic receptors at the luteal phase of the menstrual cycle in schizophrenic patients could account for an increase in psychotic findings (19). Similarly, in a study conducted in monkeys, it was found that there was an increase of 12% in dopamine receptor sensitivity in the striatum during the luteal phase compared with that during the follicular phase (20). Additionally, in functional MRI studies, it was shown that estrogen reduces the reaction in response to stress (21). This indicates that psychotic findings triggered with stress may come up with a decrease in estrogen levels (22). Riecher-Rössler et al. (17) showed that there is a

increase in estrogen levels. Halari et al. (23) also showed that there is a relation between high estrogen levels and low positive symptom intensity in schizophrenic patients. In addition, there is a study mentioning that there exists aggravation in the findings related to mood, in particular, independent of the menstrual phase in schizophrenic patients. This situation may be premenstrual dysphoric disorder added to the psychotic findings, and no increase was found in psychotic findings dependent on hormonal change (24). In their wide sampling studies with premenopausal schizophrenia-diagnosed patients, Bergemann et al. (25) showed that psychiatric applications were higher during the perimenstrual period when the estrogen levels are low.

To distinguish between an increase in the severity of the disease observed during the menstrual cycle in schizophrenia and the menstrual psychosis concept seen related only with menstruation, Brockington defined characteristics of menstrual psychosis. Accordingly, a sudden initiation, short psychotic period and full recovery, confusion during the psychotic period, stupor, mutism, delusions, hallucinations or manic symptoms, and psychotic period in parallel to the menstrual cycle, i.e., usually once a month, should be expected in menstrual psychosis (26). In some cases, it was reported that psychotic findings initiate during the second half of the menstrual cycle and terminate with menstruation, whereas in some others, psychotic findings are observed during the perimenstrual period. Menstrual psychosis cases observed during the ovulation period in the middle of the menstrual cycle, though rare, are defined in literature (18,26).

Menstrual psychosis is a disorder usually starting during the early adolescence period, in most cases initiating a psychotic period during which no psychosocial stress factor is defined. However, cases were reported describing significant stress factors prior to the first psychotic period in menstrual psychosis. Generally, no family history was defined. There is not enough response to the antipsychotic treatment in menstrual psychosis (27). In the scope of these characteristics, we considered that our patient, who was followed-up because of a diagnosis of schizophrenia and treated with antipsychotic therapy for the past two decades, should be diagnosed schizophrenia blazed with menstrual cycle but not menstrual psychosis because her symptoms are consistent and intensify during menstruation, in particular. The fact that our patient has no family history, there is no identified psychosocial stress factor initiating psychotic period, and the first psychotic period started during the early adolescence period could make us think that there are common characteristics among the schizophrenic patients whose findings are intensified with the menstrual cycle and menstrual psychosis.

During the treatment of our patient, quetiapine was favored, which has a relatively lower effect on prolactin, and the dose was increased during the periods when psychotic findings dependent on the menstrual cycle were severe, and augmentation therapy was performed with a second antipsychotic. It is reported in late-initiated female schizophrenic patients, in particular, that estrogen augmentation therapies could be appropriate (28). Stein et al. (29) reported a case in which antipsychotic treatment was not effective in menstrual psychosis and in which they established an improvement in psychotic findings with estrogen–progesterone combined treatment. In female patients with schizophrenia, questioning the severity of psychotic findings is of great importance during the menstrual cycle. If there are findings of depression and anxiety, selective serotonin reuptake inhibitors may be used. It may be effective to increase the dose of an antipsychotic that would not increase prolactin secretion 3–5 days before menstruation in patients whose psychotic symptoms intensified. Besides, hormone therapy or menstrual cycle suppression is to be considered among other options. Selective estrogen receptor modulators, which may

be effective on estrogen receptors, in the brain, in particular, could be used in psychotic disorders related to the menstrual cycle (18,30).

In conclusion, we propose that psychiatrists should definitely assess the relation between the findings of female schizophrenic patients and of female patients who have cyclical psychotic symptoms and the menstrual cycle. Wide controlled sampling studies are required for schizophrenic patients whose severity of disease increases with the menstrual cycle and for patients diagnosed with menstrual psychosis.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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